

PATENT COOPERATION TREATY

PCT



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 28 FEB 2005

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Applicant's or agent's file reference PR/4-33150AUSN		FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/EP2004/003479	International filing date (day/month/year) 01.04.2004	Priority date (day/month/year) 02.04.2003	
International Patent Classification (IPC) or national classification and IPC C07D215/26			
Applicant NOVARTIS AG et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 18.09.2004		Date of completion of this report 24.02.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Fink, D Telephone No. +49 89 2399-8701 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/003479

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-32 as originally filed

Claims, Numbers

1-12 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.:
PCT/EP2004/003479

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	12
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2004/003479

Re Item V.

the following documents are referred to in this communication:

- D1:** WO-A-95/25104 (1995-09-21);
- D2:** European Journal of Medicinal Chemistry **19**(4), 341-346 (1984);
- D3:** EP-A-0052016 (1982-05-19);
- D4:** ES-A-8605239 (1986-08-16);
- D5:** Applied Catalysis A: General, **215**(1-2), 185-190 (2001);
- D6:** WO-A-00/75114 (2000-12-14);
- D7:** WO-A-03/042160 (2003-05-22);

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document.

If it later turns out that this is not correct, the document **D7** as cited in the International Search Report could become relevant.

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-12** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The process of the present independent **claim 1** is novel over the process disclosed in **D1** (cf., page 16, "Procedure 1") on account of the present steps (a) (acylation) and (b) (reaction with a compound R-L), over

D2 (cf., page 341, column 2, last paragraph; and page 343, column 2, fourth paragraph) on account of the present steps (a) (acylation) and (c) (halogenation), and over

D3 (cf., page 13, line 1 - page 14, line 23) and **D4** (cf., page 3; and example 1) on account of the present steps (b) (reaction with a compound R-L) and (c) (halogenation).

The documents **D5** and **D6** do not disclose processes for the preparation of 5-(α -haloacetyl)-8-(substituted oxy)-(1H)-quinolin-2-ones (cf., the present claim 1).

The present process **claim 12** comprises the process according to the present claim 1 (cf., the steps (a) - (c)) and is therefore also novel over the **D1 - D6**.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-11** does not appear to involve an inventive step (Rule 65(1)(2) PCT):

Document **D1** - which represents the **closest prior art** - teaches (cf., page 16, "Procedure 1") a process for the preparation of 8-Benzyloxy-5-(α -chloroacetyl)-(1H)-quinolin-2-one which comprises halogenating 5-Acetyl-8-benzyloxy-(1H)-quinolin-2-one in 1,2-dichloroethane / methanol with benzyltrimethylammonium dichloriodate at 60 °C.

As regards the preparation of the starting compound 5-Acetyl-8-benzyloxy-(1H)-quinolin-2-one **D1** refers to the document **D2** (cf., page 7, lines 17-20 of **D1**).

The process of the present **claim 1** differs from the aforesaid process of **D1** only in the present steps (a) (acylation) and (b) (reaction with a compound R-L).

In the light of **D1** the **problem** to be solved by the present application resides in the provision of a further process for the preparation of 5-(α -haloacetyl)-8-(substituted oxy)-(1H)-quinolin-2-ones.

Accordingly, the present application proposes the process of the present **claim 1** in order to solve the given problem.

This solution, however, has to be regarded to be obvious in the light of the prior art **D1 - D3** for the following reasons:

As the prior art **D3** (cf., page 13, line 1 - page 14, line 23) and **D2** (cf., page 341, column 2, last paragraph; and page 343, column 2, fourth paragraph) already disclose

- (i) the preparation of 5-Acetyl-8-hydroxy-(1H)-quinolin-2-one by reacting 8-Hydroxy-(1H)-quinolin-2-one (cf., **D1**: the Reaction Scheme-4: the compound of the general formula (IV) wherein R^1 and R^7 represent hydrogen) with acetyl chloride (cf., **D1**: the Reaction Scheme-4: the compound of the general formula (VI) wherein R^6 represents hydrogen and X^3 chlorine) in the presence of a Lewis acid such as aluminium chloride (cf., page 14, lines 2-4 and 20-23), and
- (ii) the preparation of 5-Acetyl-8-benzyloxy-(1H)-quinolin-2-one by reacting 5-Acetyl-8-Hydroxy-(1H)-quinolin-2-one with benzylchloride (cf., **D2**: page 341, column 2, last paragraph; and page 343, column 2, fourth paragraph),

it is considered that it was obvious to the person skilled in the art to simply combine the acylation step **known** from **D3** and the alkylation (or protection) step **known** from **D2** with the halogenation step **known** from **D1** (see above) in order to solve the given problem (the more so as, the closest prior art **D1** already contains a reference to the preparation of 5-Acetyl-8-benzyloxy-(1H)-quinolin-2-one according to **D2** (cf., page 7, lines 17-20 of **D1**)).

[It is further noted that **D4** also describes (cf., the example 1) the preparation of 5-Acetyl-8-hydroxy-(1H)-quinolin-2-one by the reaction of 8-Hydroxy-(1H)-quinolin-2-one and acetyl chloride in the presence of aluminium chloride (cf., the (general) teaching **D3**).]

Having regard to the teaching of the prior art **D1** - **D5** it is considered that the dependent **claims 2-11** do not comprise any features which, in combination with the features of claim 1 to which they refer, meet the criteria of the PCT in respect of inventive step (Article 33(3) PCT).

It is therefore considered that the present **claims 1-11** do not involve an inventive step as set forth in Article 33(3) PCT.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-12** concerns chemical processes and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

- 4.1. The documents **D1 - D6** should have been cited (Rule 5.1(a)(ii) PCT).
- 4.2. Claim 12 - which is drafted as an independent process claims - comprises all the features of independent process claim 1 (cf., the steps (a) - (c)), and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).
- 4.3. Claim 1 is unclear in that the compound of the formula RL (cf., step (b)) is not clearly defined (the terms "protecting group" (R) and "leaving group" (L) do not comprise any information in respect of the structure of the compounds concerned) (Article 6 PCT).
- 4.4. The use of the relative term "about" (cf. the present claim 11) leaves the skilled person in doubt as to the lower and the upper limits of the given temperature range, thus rendering the scope of the said claim unclear (Article 6 PCT).
- 4.5. The explanation of the term "aryl" as given on page 3 (cf. lines 3-5) - as far as the optional substitution is concerned - does not correspond with the usual meaning of this term (the person skilled in the art would not understand the term "aryl" also including *substituted* aryl groups).
This creates an inconsistency between the claims and the description, which leads to a doubt concerning the extent of protection afforded by the claims, thus rendering the claims unclear (Article 6 PCT).